Remarks

Prior to entry of this amendment, claims 1-4, 6-8, 10-14, and 21-33 were pending in the application. Claim 7 is canceled herein. Applicants expressly reserve the right to pursue protection of any or all of the canceled subject matter in one or more continuing applications.

Claims 6 and 10 are amended herein. Claim 6 has been amended to incorporate the limitations of claim 7. Claim 10 has been amended to correct dependency, specifically to depend from claim 6. Support for these amendments may be found throughout the specification.

The specification is amended herein to correct typographical errors, to remove embedded hyperlinks, and to add an Abstact on a separate page.

No new matter is introduced by the foregoing amendments or the new claim. After entry of this amendment, **claims 1-4, 6, 8, 10-13 and 21-33 are pending in this application.** Consideration of the pending claims is requested.

Specification

The specification was objected to because it contained hyperlinks and typographical errors. The specification was also objected to because the abstract did not begin on a separate page. Pages 17, 44, and 45 are amended herein, thereby rendering the objection moot. The specification is also amended herein to include an abstract on a separate page, rendering the objection moot. Furthermore, page 48 of the specification is amended herein to refer to the ATCC Accession numbers.

Claim Objection

The Office action objects to claim 10 for depending on a canceled claim. Claim 10 is amended herein to depend from claim 6, rendering the objection moot.

Rejection Under 35 USC § 112, Second Paragraph

Claims 6-8 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for indicating that a framework region comprises a CDR. Claim 6 is amended herein

to clarify that the variable region comprises both the framework regions and the CDRs, thereby overcoming the rejection. Claim 7 is canceled herein, rendering the rejection moot.

Rejections Under 35 USC § 112, First Paragraph

Claims 1-4, 6-8, 10-13 and 21-23 were rejected under 35 U.S.C. 112, first paragraph as allegedly not being enabled by the specification. Claim 7 is canceled herein, rendering the rejection moot as applied to this claim. Applicants respectfully disagree with this assertion as applied to the claims as amended.

The Office action alleges that it is unclear if the antibody 8H9 is publicly available, and suggests that a deposit be made in accordance with the Budapest Treaty. Example 2 (page 48, lines 16-18) of the specification states "DNA encoding V_L protein and the V_H-PE38 protein were deposit with the American Type Culture Collection (ATCC) as Accession Nos. PTA-5661 and PTA-5660, respectively, in accordance with the Budapest treaty on November 24, 2003." Enclosed is a copy of the ATCC Deposit Receipt, documenting that the DNA encoding the 8H9-V_L (variable light chain of 8H9) was deposited in accordance with the Budapest treaty as Accession No. PTA-5661, and that the DNA encoding the 8H9-V_H-PE38 (variable heavy chain of 8H9), was deposited in accordance with the Budapest Treaty as Accession No. PTO-5660. Also enclosed is a copy of Form PCT/RO/134 that was published with the parent PCT application; this form acknowledges that the International Bureau has reviewed the deposit information for PTA-5660 and PTA-5661. As DNA encoding both the light and the heavy chain of 8H9 have been deposited with the ATCC in accordance with the Budapeast Treaty, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-8 and 10-12 were rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled by the specification, as allegedly any antibody with a single CDR from 8H9 would not bind the 8H9 antigen. Claim 7 is canceled herein rendering the rejection moot as applied to this claim. Applicants respectfully disagree with this rejection as applied to claims 6, 8 and 10-12.

The Office action acknowledges that the specification is enabled for an isolated Fv protein comprising a heavy chain variable region that includes the HCDR1 of residues 31-35 of

SEQ ID NO: 3, the HCDR2 of residues 50-60 of SEQ ID NO: 3, the HCDR3 of residues 99-107 of SEQ ID NO: 3, and comprising a light chain variable region that includes the LCDR1 of residues 157-167 of SEQ ID NO: 3, the LCDR2 of residues 183-189 of SEQ ID NO: 3, and the LCDR3 of residues 222-230 of SEQ ID NO: 3. Thus, solely to advance prosecution, claim 6 is amended herein to clarify that the claimed antibodies include three H-CDRs and three L-CDRs. Claims 8 and 10-12 depend from claim 6, or a dependent claim thereof. Applicants believe that the amendment of claim 6 overcomes the rejection.

Rejections Under 37 USC § 103

Claims 1-4, 6-8, 10-13 and 21-23 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Modak et al. (Cancer Res. 61: 4048-4054, 2001) in view of U.S. Patent No. 5,618,920 (Robinson et al.) and Reiter et al. (Biochemistry 33: 5451-5459, 1994) and U.S. Patent No. 5,530,101 (Queen et al.). Claims 1-3, 6-8, 10-12 and 21-23 were rejected under 35 U.S.C. § 103 (a) as allegedly being obvious over U.S. Published Patent Application No. 2002/102264 (Cheung[a]), in view of Robinson et al. and Queen et al. Claims 1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Published Patent Application No. 2003/0103933 (Cheung [b]) in view of Robinson, Reiter et al. and Queen et al. Claims 1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. § 103 (a) as allegedly being obvious over U.S. Published Patent Application No. 2005/0169932 A1 (Cheung[c]) in view of Robinson et al., Reiter et al., and Queen et al. Claims 7 is canceled herein, rendering the rejections moot as applied to this claim. Applicants respectfully disagree with these rejections as applied to claims 1-4, 6, 8, 10-13 and 21-23.

The Office action alleges that Modak et al., Cheung[a], Cheung[b], and Cheung[c] all teach a hymbridoma that produce monoclonal antibody 8H9 and a scFv form of 8H9. The Office action acknowledges that none of Modak et al., Cheung[a], Cheung[b] or Cheung[c] teach a dsFv form of 8H9. The Office action alleges that in view Queen et al., Reiter et al. and Robinson et al., the production of a dsFv form of 8H9 PE38 would be obvious from the cited prior art.

To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations (MPEP § 2143).

Applicants contend that the Office action has failed to establish a motivation to combine the cited references. The mere fact that a reference can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. [emphasis added] *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Even if *arguendo* a *prima facie* case of obviousness was made, evidence of unobvious or unexpected advantageous properties, even a superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness MPEP §716.02(a). "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). In the present case, there is nothing in any of the prior art references that suggests that a dsFv form of 8H9 would be less toxic *in vivo*.

MPEP § 716.02(b) sets forth that evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims (see also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). *In re Blondel*, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and *In re Fouche*, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) are examples of cases where indirect comparative testing was found sufficient to rebut a *prima facie* case of obviousness).

Submitted herewith is the Declaration of Dr. Pastan Under 37 C.F.R. § 1.132 (hereinafter "Declaration") documenting the unexpectedly superior properties of the dsFv form of 8H9 linked to a toxin (*Pseudomonas* exotoxin, PE38) as compared to the scFv form of 8H9 linked to a PE38. This Declaration documents the unexpected finding (that could not be predicted based on the Modak et al., Cheung[a], Cheung[b], and Cheung[c]), that the dsFv form showed substantially less toxicity than the scFv form.

Specifically, the Declaration documents that when the dsFv and the scFv forms of monoclonal antibody 8H9 were produced the final yield of 8H9(dsFv)-PE38 was unexpectedly much higher than the final yield of 8H9(scFv)-PE38. Specifically, the final yield of 8H9(dsFv)-PE38 was16%, while the final yield of the scFv form was 1.7 mg or 1.7%. In addition, when the cytotoxicity of the two antibodies was tested, the *in vivo* toxicity of 8H9(dsFv)-PE38 unexpectedly was substantially less than the toxicity of 8H9(scFv). The LD_{50} of 8H9(scFv)-

PE38 was less than 0.2 mg/ml, while the LD_{50} of 8H9(dsFv)-PE38 was 1.0 to 0.75 mg/ml. It was confirmed that 8H9(scFv)-PE38 was not toxic in primates. This finding of an unexpectedly superior result of the 8H9(dsFv)-PE38 as compared to 8H9(scFv)-PE38, namely higher yield and reduced toxicity of the dsFv form, overcomes any prima facie case of obviousness.

In view of the Declaration documenting the unexpectedly superior results obtained with the dsFv form of 8H9, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

Obviousness-Type Double Patenting

Claims 1-3, 6-8, 10-13 and 21-23 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-2, 4, 6-7, 9, 11 and 52-54 of U.S. Patent Application No. 10/097,558 alone or in view of Reiter et al. Claims 1-3, 6-8, 10-13 and 21-23 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11 and 18-23 of U.S. Patent Application No. 10/505,658 alone or in view of Reiter et al.

Applicants respectfully disagree with these rejections. The Declaration of Dr. Pastan documents the non-obvious nature of the presently claimed subject matter.

Neither U.S. Patent Application No. 10/097,558 or U.S. Patent Application No. 10/505,658 have been allowed. Thus, Applicants request that these rejections be held in abeyance until the time that subject matter is considered to be allowable.

Request for Interview and Conclusion

If an additional rejection is asserted, or if the present rejections are maintained, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request. It is respectfully submitted that the present claims are in a condition for allowance.

Respectfully submitted,

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By _____
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4239-67287

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.

To: (Name and Address of Depositor or Attorney)

NIH
Attn: Ira H. Pastan
Bldg. 37, Room 5106A
37 Convent Drive
Bethesda, MD 20892

COPY

Deposited on Behalf of: The Government of the United States of America as represented by the Secretary of the Department of Health and Human Services

Identification Reference by Depositor:	**Patent Deposit Designation**
Plasmid: 8H9-V_H-PE38	PTA-5660
Plasmid: 8H9-V_L	PTA-5661

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received November 25, 2003 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested December 5, 2003. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Marie Harris

Marie Harris, Patent Specialist, ATCC Patent Depository

Date: December 23, 2003

cc: William D. Noonan, M.D.
Ref: Docket or Case No.: 4239-67287